IRIS Assessment Plan for Ethylbenzene

Presentation to the
Science Advisory Board Chemical Assessment Advisory Committee
September 28, 2017

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Outline of the Presentation

- Background
- Scoping Summary
- Initial Problem Formulation
- Overall Objective, Specific Aims and PECO Framework
- Assessment Approach
- Key Science Issues

Background: Physical-Chemical Properties

- Aromatic hydrocarbon with sweet odor
- Colorless flammable liquid
- Heavier than air but lighter than water
- Poor water solubility

Background: Sources and Uses

- Found naturally in petroleum
- Constituent in naphtha, asphalt
- Generated via several catalytic chemical reactions
- Used in transportation fuels (gasoline, marine and aviation fuels)
- Industrial solvent (paints, inks, varnishes, other surface coatings)
- Greatest use as chemical intermediate in the production of styrene

Background: Existing Ethylbenzene IRIS Assessment

- Oral RfD last revised in 1987; based on hepatic and renal toxicity
- Carcinogenicity Assessment last revised in 1988; cancer values not determined due to lack of data
- Inhalation RfC last revised in 1991; based on developmental toxicity

Background: Exposure to Ethylbenzene

General population

Contact with gasoline or gasoline engine exhaust, use of solvents, inks, various surface coating products, tobacco smoke

Occupational

Petroleum industry, production of styrene, manufacturing and processing facilities of solvents and surface coatings with ethylbenzene as ingredient, any occupation exposed to gasoline or gasoline engine exhaust (gas stations, tunnel workers, highway workers, parking lot workers)

Susceptible populations

Workers in facilities that make or use ethylbenzene or products containing ethylbenzene; individuals living near manufacturing and processing facilities, petroleum refineries, hazardous waste sites, major highways. Additional high risk populations are individuals exposed to ethylbenzene-contaminated water sources such as wells downstream of uncontrolled land fills, hazardous waste sites and leaking underground storage tanks.

Scoping Summary

In 2014 the IRIS Program held it's initial Scoping and Problem Formulation public meeting for ethylbenzene. Since that time, the IRIS Program has reaffirmed the specific assessment needs of the interested program offices.

Scoping Summary (con't)

EPA Program or regional office	Oral	Inhalation	Statutes / Regulations	Anticipated Uses / Interest
OLEM	✓	✓	Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) – Section 102	Ethylbenzene toxicity values are needed to set risk-based screening levels, derive baseline risks, establish clean-up levels, and evaluate clean-up progress at contaminated sites.
EPA Regions	✓	✓		
OW	✓		Clean Water Act (CWA) – Sections 304 / 307	Ethylbenzene is identified as a toxic pollutant under section 307 of the CWA.
OAR		✓	Clean Air Act (CAA) – Section 112	Ethylbenzene is classified as a hazardous air pollutant (HAP) under the CAA. OAR is mandated under the CAA to periodically conduct risk and technology reviews (RTRs) for HAPs. Toxicity values are needed to evaluate residual risk.
OCSPP	✓	✓	Toxic Substances Control Act (TSCA) – Section 6(b)	Ethylbenzene was identified in the TSCA Work Plan for Chemical Assessments.
OLEM (Office of Land and Emergency Management); OW (Office of Water); OAR (Office of Air and Radiation); OCSPP (Office of Chemical Safety and Pollution Prevention)				

IAPs Represent Continuous Refinement of Scoping and Problem Formulation Materials

07/2014 Ethylbenzene Scoping & Problem Formulation Document	09/2017 Ethylbenzene Assessment Plan Document
Introduction and background	Introduction and background
Production and use, human exposure pathways, environmental fate	Concise discussion to extent this information provides necessary context
Scoping (“Scope of the Assessment”)	Scoping (“Scoping Summary”)
[Not explicitly discussed]	Table of Agency Interest
Problem Formulation	Problem Formulation
Preliminary Literature Survey (conducted by manual review of studies retrieved)	Preliminary Literature Survey (conducted using various approaches, e.g. machine-learning, prior assessments)
Systematic Review Elements	Systematic Review Elements
[Not explicitly discussed]	Specific Aims
Hazard Questions for Systematic Review	Draft Populations, Exposures, Comparators, Outcomes (PECO) Framework
[Not explicitly discussed]	Assessment Approach
Key Issues	Key Science Issues

Initial Problem Formulation

	Human Studies		Animal Studies		In Vitro Studies
	Oral	Inhalation	Oral	Inhalation	
Health Outcomes					
Body Weight Effects				✓ (Subchronic)	
Cancer		✓ (Occupational)	✓ (Chronic)	✓ (Chronic)	
Cardiovascular			✓ (Subchronic)	✓ (Subchronic, Chronic)	
Dermal				✓ (Chronic)	
Developmental				✓ (Subchronic)	
Endocrine				✓ (Subchronic, Chronic)	
Gastrointestinal				✓ (Subchronic, Chronic)	
Hematological		✓ (Occupational)	✓ (Subchronic)	✓ (Subchronic, Chronic)	
Hepatic			✓ (Subchronic)	✓ (Subchronic, Chronic)	
Immunological				✓ (Subchronic)	
Metabolic disease					
Musculoskeletal				✓ (Subchronic, Chronic)	
Neurological and Sensory		✓ (Occupational)	✓ (Subchronic)	✓ (Subchronic)	✓
Renal			✓ (Subchronic)	✓ (Subchronic, Chronic)	
Reproductive			✓ (Subchronic)	✓ (Subchronic)	
Respiratory		✓ (Community)	✓ (Subchronic)	✓ (Subchronic, Chronic)	
Other Data and Analyses					
ADME		✓	✓	✓	
Toxicokinetic models					✓
Mode-of-action hypotheses					✓
Susceptibility data		✓			
Genotoxicity		✓	✓	✓	✓
Other mechanistic data					✓

Source: U.S. EPA. IRIS Toxicological Review of Ethylbenzene (Scoping and Problem Formulation Materials). U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-14/198, 2014. https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=308400

Overall Objective

The overall objective of this assessment is to identify adverse health effects and characterize exposure-response relationships for ethylbenzene to support development of toxicity values.

Specific Aims

- **Identify** literature reporting exposure to ethylbenzene as outlined in the PECO framework.
- **Identify** mechanistic studies for use in understanding potential human health hazards.
- **Conduct** study evaluations (risk of bias and sensitivity) for individual human and animal studies.
- **Extract** data on relevant health outcomes from human and animal studies based on the study evaluation.
- **Synthesize** the evidence across studies assessing similar health outcomes.

Specific Aims (con't)

- **Express** confidence in conclusions from across studies (or sub-sets of studies) within human and animal evidence streams for each health outcome.
- **Integrate** results across evidence streams for each health outcome to conclude whether a substance is hazardous to humans.
- **Identify** and discuss issues concerning potentially susceptible populations and life stages.
- **Derive** toxicity values (e.g., RfDs, RfC, cancer risk values) as supported by the available data.
- **Characterize** uncertainties and identify key data gaps and research needs.

PECO Framework

PECO Element	Evidence
Populations	**Human:** All populations and life stages.
	Animal: Non-human mammalian animal species (whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal and adult stages).
	In vitro: Non-mammalian model systems; Human or animal cells, tissues, or biochemical reactions with in vitro exposure regimens; bioinformatics pathways of disease analysis; or high throughput screening data.
Exposures	**Human:** Exposure to ethylbenzene, including occupational exposures, alone or as a mixture by any route.
	Animal: Exposure to ethylbenzene alone by any route.
	In vitro: Exposure to ethylbenzene via growth or assay medium.
Comparators	**Human:** Any comparison or reference group exposed to; lower levels of ethylbenzene, no exposure to ethylbenzene, or to ethylbenzene for shorter periods of time.
	Animal: Quantitative exposure versus lower or no exposure with concurrent vehicle control group.
	In vitro: Quantitative exposure versus lower or no exposure with concurrent vehicle control group.
Outcomes	All health outcomes (both cancer and noncancer).

	Cardiovascular	Dermal	Developmental	Endocrine/ Exocrine	Gastrointestinal	Hematological	Hepatic	Immunological	Musculoskeletal	Nasal	Neurological	Pulmonary	Renal	Reproductive	Ocular	Other effects[a]
Human studies – inhalation exposure																
Occupational Epidemiological Studies						1 0	1 0				1 1					
General Population Epidemiological Studies	1 1	2 0	5 2		1 0		1 0	9 7		2 0	2 0	4 2			2 1	2 2
Controlled Exposure Studies								1 0		7 6					5 4	2 2
Case Reports and Case Series Reports																
Human studies – oral exposure – None identified																
Human studies – dermal/multiple routes or unknown (biomarker) exposure																
Occupational Epidemiological Studies						1 0	1 0									1 0
General Population Epidemiological Studies	1 1						1 0	1 1				2 1				1 0
Controlled Exposure Studies																
Case Reports and Case Series Reports											1 0					

[a] Other effects include irritation, clinical signs, and neoplasia (not organ specific).

Heat map key:

Number of studies that examined the endpoint

Number of studies reporting response measurements from ethylbenzene exposure

	Cardiovascular	Dermal	Developmental	Endocrine/ Exocrine	Gastrointestinal	Hematological	Hepatic	Immunological	Musculoskeletal	Nasal	Neurological	Pulmonary	Renal	Reproductive	Ocular	Other effects[a]
Animal studies - inhalation exposure																
Chronic	6	2		6	2	6	7	6	2	2	2	6	6	6	2	7
	0	0		1	0	0	5	0	0	0	0	1	2	3	0	4
Subchronic	3	1		3	3	3	6	3	2	3	4	3	7	3	3	7
	0	0		0	0	0	6	1	0	0	1	1	6	0	0	1
Short-term	9	4	1	8	6	7	17	9	6	9	18	13	16	10	7	23
	0	0	0	1	0	2	10	0	0	0	9	2	5	0	0	8
Acute										1	4	3			1	2
										1	4	3			1	2
Multigenerational			3				3						3	3		3
			1				2						2	1		1
Gestational	2		12	2			6	5			2	5	6	12		11
	0		10	0			4	3			0	0	3	3		4
Animal studies - oral exposure																
Chronic	2			2	1	1	2	2	1	1	1	2	2	2		2
	0			0	0	0	1	0	0	1	0	0	1	0	0	1
Subchronic	1	1		1	1	1	2	1	2	1	2	1	2	1	2	2
	0	0		0	0	1	2	1	0	0	0	0	2	0	0	2
Short-term	1			1		1	2	1			1		1	2		2
	0			0		0	1	0			0		1	1		2
Acute					1		1					1				1
					1		1					1				1

[a] Other includes body weight, clinical signs, and other observations.

Heat map key:

Number of studies that examined the endpoint

Number of studies reporting response measurements from ethylbenzene exposure

Assessment Approach

Modular Approach

- Components: RfC, RfD, Cancer assessment (Inhalation slope factor, oral slope factor, qualitative description).
- Stand alone products – Allows flexibility in providing needed toxicity values without being delayed by other component issues.
- Ethylbenzene plan is to develop RfCs using the latest tools available (BMDS).
- Given the very limited oral database for ethylbenzene, PBPK modeling may be useful for route to route extrapolation in deriving an RfD.
- Cancer assessment: Interpretation of animal data will require extensive work.

Key Science Issues

The preliminary literature survey identified the following key scientific issues, including potential mode-of-action hypotheses that warrant evaluation in the assessment.

- Toxicokinetics of ethylbenzene (sex, species and strain differences in metabolism, etc)
- Mouse lung toxicity / tumors (Mouse lung tumor workshop)[1]
- Rat renal toxicity / tumors (tBA[2,3] , ETBE[3])
- Mechanisms of neurotoxicity including ototoxicity
  - Reversibility, persistence and/or potential for progression of the neurobehavioral or ototoxic effects
  - The relevance of ototoxicity to humans at lower exposure levels

[1] USEPA Summary Report: State-of-the-Science Workshop on Chemically-Induced Mouse Lung Tumors: Applications to Human Health Assessments. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=291094

[2] Integrated Risk Information System (IRIS) Public Science Meeting, June 29-30, 2016 for Benzo[a]pyrene and tert-Butyl Alcohol

[3] Public Meeting of the SAB-Chemical Assessment Advisory Committee Augmented for the review of Ethyl Tertiary Butyl Ether (ETBE) and tert Butyl Alcohol (tert-butanol; tBA), 08/15/2017 to 08/17/2017

The End

Questions?